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Shimane Medical University Clinico-Pharmaco-Pathological Conference

A CASE OF REFLUX ESOPHAGITIS WITH DUODENAL ULCER AND HYPERGASTRINEMIA: A RECORD OF SHIMANE MEDICAL UNIVERSITY CLINICAL, PHARMACOLOGICAL AND PATHOLOGICAL CONFERENCE FOR MEDICAL STUDENTS (CPPC)

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1. PRESENTATION OF THE CASE

A 91-yr-old woman was admitted to Shimane Medical University Hospital (SMUH) with the complaint of hematemesis. She had been bedridden for 10 years with left-sided hemiplegia and dementia caused by a putaminal hemorrhage. Two days before the admission, brown-colored vomit was noticed on her bed, and on the following day, she also vomited coffee-ground contents during her meal. Then she was referred to SMUH by her family physician for further diagnosis and treatment.

On physical examination, she was found febrile, lean, and apathic. Her blood pressure was 170/100 mmHg, pulse 110/min and temperature was elevated to 38.4℃. However, no pathological signs could be found on abdomen examination. Laboratory investigations showed normal hemoglobin (13.1 g/dl), mild-leukocytosis (13,100/μl), and a low serum albumin level (3.2 g/dl). Blood urea nitrogen (BUN) was 45 mg/dl while serum creatinine was not elevated (0.45 mg/dl). Serum electrolytes (Na^+, K^+, Cl^-, Ca^{++}, P) were also within normal ranges. Emergency upper gastrointestinal endoscopy on admission revealed a high-grade (Los Angeles grade D) reflux esophagitis with active bleeding from esophageal erosion. An open ulcer was also found in the duodenal bulb. She was diagnosed as a case of reflux esophagitis with duodenal ulcer, and proton pump inhibitor was given as treatment. After the symptomatic recovery, she was discharged from the hospital and remained under the follow-up of her family physician.

However, instead of continuing the treatment with proton pump inhibitor, one month later, she had again coffee-ground vomiting and was readmitted to SMUH. Although she was febrile, no respiratory symptom including cough and wheezing was noticed. Chest X-ray revealed pneumonia possibly caused by aspiration of vomits and upper gastrointestinal endoscopy showed the high grade reflux esophagitis as detected earlier. On further laboratory investigation after the second admission, elevated levels of CEA (8.8 ng/ml), CA19-9 (785 U/ml) and Span-I (204 ng/ml) was detected. In addition to these tumor markers of an adenocarcinoma, her serum gastrin level was found remarkably high (1,015 pg/ml). Repeated tests on serum gastrin revealed a fluctuation in the level ranging from 200 to 1540 pg/ml. Direct measurement of gastric acid secretion before and after the administration of pentagastrin showed an increased BAO/MAO (basal acid output/maximal acid output) ratio, suggesting a higher endogenous serum gastrin level. Secretin loading test did not show any paradoxical rise of serum gastrin level rather depressed after intravenous secretin administration. CT scan of abdomen revealed a tumor in the head of the pancreas (Fig. 1). The border of the tumor was indistinct which could not be homogeneously enhanced by contrast. In the center of the tumor, irregular shaped unenhanced area was found. Although the common bile duct was not dilated, pancreatic duct was found dilated. The CT scan also revealed thickening of gastric mucosa with abundant blood supply and suggested the absence of gastric mucosal atrophy. From the radiological examination, surgical excision of the pancreatic tumor was recommended.

Surgical excision of the pancreatic tumor, however, was not considered due to her general physical condition. She was therefore symptomatically treated with a proton pump inhibitor for reflux esophagitis and

duodenal ulcer. With symptomatic improvement, she was transferred to another hospital for medical treatment of the pancreatic tumor and associated reflux esophagitis with duodenal ulcer. She recovered and stayed in good condition for three weeks. After that, she became febrile and her laboratory investigations suggested the possible damages in the hepatobiliary system. Finally, she died of septicemia and possible endotoxin-shock in a month.

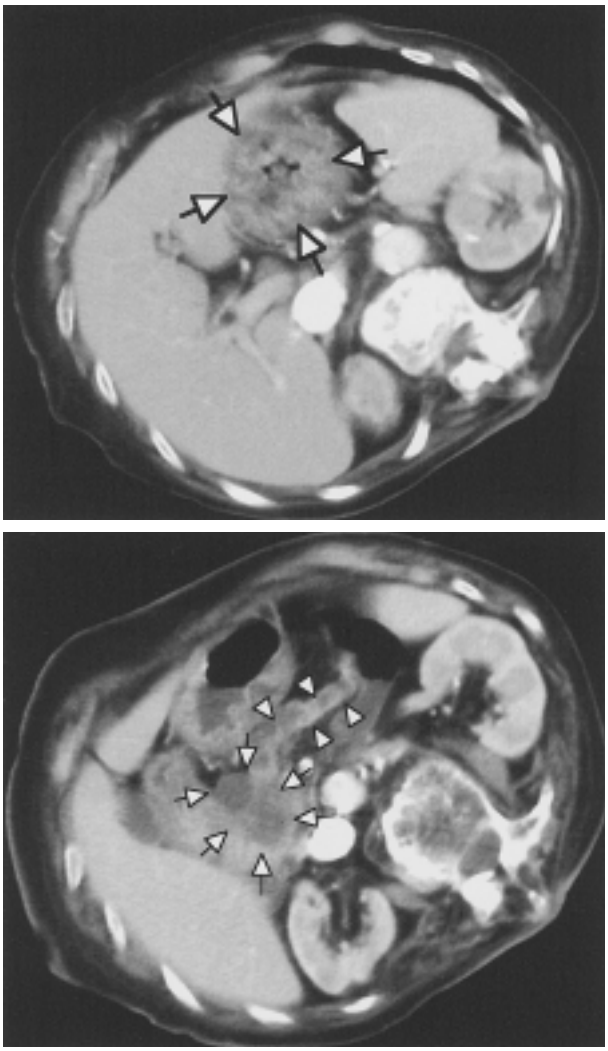

Fig. 1. Abdominal CT scan revealed thickened gastric mucosa (arrows) which is densely enhanced by a contrast enhancement (upper panel). A tumor was found in the head of the pancreas (arrows) and the pancreatic duct (arrow heads) was dilated (lower panel).

2. DIFFERENTIAL DIAGNOSIS

Medical Student A:

Reflux esophagitis and duodenal ulcer are quite common which are related to increased gastric acid secretion. The prevalence of reflux esophagitis has increased in Japan during last 20 years. The recent reports show that approximately 10% of the persons who visit annual health check up for the screening of gastric cancer have endoscopically-identifiable reflux esophagitis. Esophagitis is endoscopically graded from A (lightest) to D (severest) according to the width of the esophageal mucosal break, and over 80% of the patients with reflux esophagitis have grade A esophagitis. This patient had grade D esophagitis that is the severest grade and possibly caused by a combined effect of impaired esophageal motor function and the higher gastric acid secretion. The esophageal motor function deteriorates with aging and has been reported to be impaired by several diseases of central nervous system including Parkinson's disease. Therefore, the putaminal hemorrhage resulting hemiplegia in this case might have some role in the development of esophagitis.

Pathogenesis of duodenal ulcers is not yet fully understood. The combination of high gastric acid output and *Helicobacter pylori* (*H. pylori*) infection is believed to be of important roles for the development of duodenal ulcers, since more than 95% of the cases with duodenal ulcers are infected with *H. pylori*. The unusual presentation of this case was that she had both a duodenal ulcer and a high-grade reflux esophagitis. There was a consensus that majority of patients with high-grade reflux esophagitis were not infected with *H. pylori*. Since the infection of *H. pylori* was not investigated in this case, it is difficult to speculate why duodenal ulcer was associated with a high-grade reflux esophagitis in this patient. The possible explanation, however, is the presence of high gastric acid secretion caused by Zollinger-Ellison syndrome. The patients with Zollinger-Ellison syndrome were, indeed, reported to develop duodenal ulcers without the infection of *H. pylori*.

Elevated serum gastrin level supported the presence of gastrinoma and Zollinger-Ellison syndrome. Elevated bioactive serum gastrin concentrations was also supported by the high ratio in BAO/MAO, since high BAO/MAO ratio indicates the basal acid secretion was almost maximally stimulated without the exogenous administration of pentagastrin. The presence of the tumor in head of the pancreas in this case also supported the diagnosis of Zollinger-Ellison syndrome. Elevated serum gastrin was observed not only

in Zollinger-Ellison syndrome but also in various other diseases including antral G cell hyperplasia, pernicious anemia, severe gastritis caused by *H. pylori* infection, and the remained antral mucosa after the gastrectomy. Since diseases other than gastrinoma and antral G cell hyperplasia were accompanied by decreased gastric acid secretion, gastrinoma and antral G cell hyperplasia were possible pathological conditions for this patient.

Staff Doctor of Gastroenterology Unit:

To differentiate gastrinoma and antral G cell hyperplasia, secretin loading test is useful. Secretin stimulates gastrin secretion from G cells via its receptor on the cell membrane, resulting cyclic AMP production. It also stimulates somatostatin secretion from D cells via its receptors. Somatostatin strongly inhibits gastrin secretion from G cells when somatostatin-secreting D cells are present near the gastrin-secreting G cells, since somatostatin works as a local hormone. Gastrinoma is a clonal tumor composed solely of gastrin-producing G cell-like tumor cells, while antral normal G cells are almost always accompanied by somatostatin-secreting D cells. Therefore, secretin, when intravenously administered, stimulates gastrin secretion from gastrinoma but it inhibits gastrin secretion from antral G cells through increased secretion of somatostatin from accompanying D cells. Secretin loading test performed in this patient showed the decrease in serum gastrin concentration and suggested against a gastrinoma but for an antral G cell hyperplasia.

Medical Student B:

A CT scan provided another important piece of information about this patient. Abdominal CT scan detected a tumor in head of the pancreas and it was not homogeneously enhanced. Predominant anatomical sites where gastrinoma develops are head of the pancreas and the proximal half of the duodenum. Therefore, the tumor found in this case was located in an anatomical site where gastrinoma is commonly found. The heterogeneous contrast enhancement and indistinct margin observed in this tumor was against the gastrinoma, since gastrinoma is a homogenous tumor with a distinct margin. The radiological characteristics including indistinct margin, heterogeneous enhancement, central unenhanced area, and dilated major pancreatic duct suggested that the tumor was a mucous-producing tubular adenocarcinoma of the pancreas. The increased serum CEA, CA19-9, and S pan-Ⅰ also supported the diagnosis of a tubular adenocarcinoma, not a gastrinoma. Small gastrinomas are difficult to be detected in the duodenum by radiological examinations such as CT scan. However, majority of patients with duodenal gastrinomas is reported to have multiple endocrine neoplasia type 1 (MEN type 1). Although MEN type 1 has hyperparathyroidism, pituitary adenoma, and pancreatic-duodenal endocrine tumors, the hyperparathyroidism appear first as a clinically overt disease. This patient had no clinical symptoms suggesting hyperparathyroidism and her serum calcium concentration was not elevated. Therefore, the possibility of duodenal gastrinomas or associate MEN type 1 may be considered low.

In summary, radiological examination as well as serological tests for tumor markers suggested the presence of pancreatic mucous-producing adenocarcinoma but findings did not support the presence of a gastrinomas in and around the pancreas.

Medical Student C:

Concerning the cause of death of this patient, the available clinical information is limited. Two possibilities, however, may be considered. Firstly, aspiration pneumonia may result septicemia, since she threw up coffee-ground vomit and gastric juice frequently. The vomiting caused by increased gastric acid secretion and impaired antireflux esophageal motor function in this case may be considered an important risk factor for chemical or bacterial aspiration pneumonia. Secondly, adenocarcinoma in head of the pancreas may cause a stenosis of common bile duct and may cause obstructive suppurative cholangitis with resulting septicemia. When common bile duct is narrowed gradually by the compression of the growing tumor, the occurrence of suppurative cholangitis is rare. But when it was obstructed suddenly by calculi or by clots, the risk of suppurative cholangitis increases. The microorganisms that cause bile duct infection are mainly gram-negative rods with lipopolysaccharide on their cell wall. The lipopolysaccharide strongly activates the inflammation and

easily induces endotoxin shock and disseminated intravascular coagulation. The clinical course, especially sudden death, suggests the obstructive suppurative cholangitis with resulting endotoxin shock as a more feasible cause of death of this case.

Staff Doctor of Gastroenterology Unit:

All the clinical information suggested the diagnosis of antral G cell hyperplasia, associated with pancreatic adenocarcinoma, resulting obstructive suppurative cholangitis. The pathogenesis of antral G cell hyperplasia is not yet understood. The interesting point in this case was the presence of pancreatic adenocarcinoma. There are several case reports that undifferentiated pancreatic cancers can produce gastrin-releasing polypeptide. Gastrin-releasing polypeptide, if produced by pancreatic cancer cells, may stimulate antral G cells and may cause hypergastrinemia.

CLINICAL DIAGNOSIS

1. Antral G cell hyperplasia.
2. Mucous producing adenocarcinoma of the pancreas.
3. Septicemia possibly caused by obstructive suppurative cholangitis.

3. REVIEWING THE MEDICATION FROM PHARMACOLOGICAL ASPECTS

The pharmacology group of students conducted careful reviewing of the case while consulting the professor of basic & clinical pharmacology, and pointed out several comments as to the therapeutic regimen that the patient underwent. The 3 majors of those comments raised were presented and discussed at the Conference, and summarized as follows.

1) Was the Use of Proton Pump Inhibitors (PPIs) Optimum?

Before we raised a problem, we describe the present case's whole procedure of the medication for gastric acid secretion.

The patients had been treated with famotidine (Gaster®, an H_2 blocker) before her 1st hospitalization, but soon thereafter it was replaced with the combination of lansoprazole (Takepron®, a PPI), cisapride (Acenalin®, a prokinetic agent) and sodium alginate (Alloid G®). After this combination was continued for a week, symptoms were improved so that the patient was once discharged (May 26). Following the discharge, the medication for reflux esophagitis consisted of lansoprazole and teprenone (Selbex®). Despite this treatment, she had recurrent hematemesis as before, and was hospitalized again to SMUH on June 21.

For the first month of the 2nd hospitalization, the patient was kept fasting so that lansoprazole could not be used because no parenteral preparation of the drug was available. Instead that, she was injected with famotidine and metoclopramide (Primperan®). When she got improved (July 19), famotidine was switched to lansoprazole and Maalox®, both of which were given as suspension via gastric tube. By this medication the gastric juice became non-hematic and its volume was stabilized, so that she was transferred to another hospital on September 8.

Immediately after the transfer, lansoprazole was replaced by omeprazole (Omepral®). On the same day or next day, she had an attack of high fever and difficulty in oral ingestion. Thus, oral omeprazole and Maalox® were stopped and she received daily-repeated injections of famotidine and metoclopramide until September 15. Then she resumed omeprazole and Maalox® via gastric tube until her penultimate day of life (September 26).

It was wondered why lansoprazole that exerted reasonable effect during the 2nd hospitalization was replaced with omeprazole after the patient was transferred to another hospital. As a general rule, the drug that proves itself fairly effective in a given patient should not be replaced with another agent even if these two drugs belong to the same class. This is because different agents have not only different potency but also different pharmacokinetic properties. In particular, lansoprazole and omeprazole preparations are substantially different in respect of their drug-delivery design (Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th ed., pp907-909). Omeprazole is an enteric-coated tablet. Thus, if a tablet is broken before ingestion via gastric tube, the compound is destroyed by gastric acid. On the other hand, lansoprazole is a gelatin-coated

capsule which contains numerous enteric-coated grains. Thus, even if the outer shell is broken before ingesting via gastric tube, enteric-coated grains will reach the intestine where they are dissolved and effectively absorbed into portal vein system. At present, there are no PPI preparations available for injection. Therefore, when oral preparations of PPIs are to be ingested via gastric tube as a suspension, it should be emphasized that omeprazole tablet should not be broken before ingestion and that lansoprazole micrograins should be kept as enteric-coated.

Anyhow, parenteral preparations of PPIs are of frequently and highly demanded, because patients with serious esophagitis and peptic ulcer should often keep fasting.

Other Discussions Related to PPIs:

It was discussed whether or not extraordinarily high levels (about 10 times of standard level) of plasma gastrin might be due to potent PPI treatment. Although no direct evidence was available for the present case, previous reports suggested that therapeutic doses of PPIs might elevate gastrin levels at most 3-4 times. In view of these data, consensus was attained that PPIs were unlikely to be the principal cause of hypergastrinemia in this case.

2) Was Antibiotic Therapy Appropriate?

The patient was febrile throughout the observation period (Fig. 2, upper panel). However the origin was unknown. Aspiration pneumonia was a suspected cause of the fever of unknown origin (FUO), but sputa examination did not prove pathogenic microbium. Hence, empirical use of intravenous flomoxef (Flumarin®, an oxacephem) was performed intermittently (Fig. 2, upper panel; Bars "A"). However, its dose and duration seems insufficient, because fever and CRP was not completely normalized. There was an argument at the Conference that the increase in BUN might have been a limitation hampering the more sufficient dose and duration of flomoxef (Fig. 2, Lower panel). Despite this argument, flomoxef was unlikely to be responsible for lowered renal function because intermittently repeated use of flomoxef was not coincided with the increases in BUN and creatinine. Instead, non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac

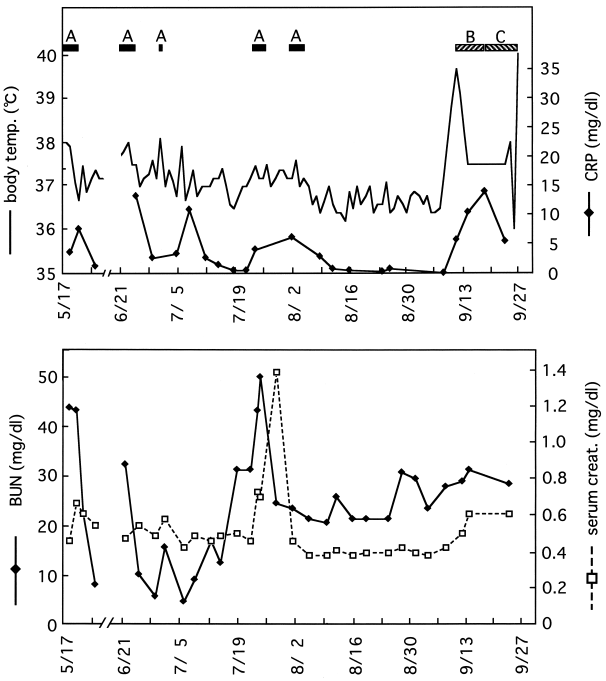

Fig. 2. Time-related changes in indices for infection/inflammation (upper panel) and renal function (lower panel) from the 1st admission day (May 17) to the death (September 27).Upper panel: Changes in body temperature and CRP (C-reactive protein). Solid bars A, and hatched bars B and C indicate the periods when chemotherapy with intravenously infused antibiotics was executed as follows. A: flomoxef-Na 1 g/day. B: cefazolin-Na 1 g b.i.d.. C: cefmetazole-Na (1 g b.i.d.) + amikacin sulfate (200 mg/day). Lower panel: Changes in BUN (blood urea nitrogen) and serum creatinine. Marked, transient increases in BUN and creatinine (peak July 26-27) and reciprocal decrease in urine volume (not shown) may be coincided with the use of NSAIDs. Due to this oliguria, furosemide (Lasix®, 20 mg/day, i.v.) was used on July 24, 25, and August 1. To be noted is that the time-scale is exactly the same as that of upper panel for convenient comparison.

(Voltaren® suppository) and ketoprofen (Menamin® supp.) that were used July 24-26 as antifebrile seemed to be the most suspicious to reduce renal blood flow and GFR.

As disclosed later by post-mortem autopsy, the FUO might be due to biliary tract infection. Therefore, origin of the fever should have been searched more cautiously, pathogen should have been identified and its susceptibility to antibiotics examined. On September 8 when severe attack with high fever occurred, a 1st-generation cepharosporin cefazolin was used, but this antibiotic seemed ineffective at all. Instead, a 3rd-generation drug cefmetazole in combination with an aminoglycoside amikacin seemed partly effective at least until the possible

occurrence of highly-resistant bacteria.

3) **Potential Adverse Effect of Antihypertensive Agent.**

Calcium channel blockers (CCB) may predispose the lower esophageal sphincter (LES) incompetence because those drugs exert general inhibitory actions onto smooth muscles and thereby decreasing the LES tone further. Therefore, the reflux esophagitis patients should avoid CCB-class antihypertensive agents and other smooth-muscle relaxants (Harrison's Principles of Internal Medicine, 14th ed., Chapter 283). The present case was prescribed imidapril (Tanatril®, an ACE-inhibitor) in combination with benidipine (Coniel®, a CCB) or nifedipine (Adalat®, a CCB) as antihypertensive agents. However, it should be emphasized that this patient should be treated with ACE inhibitor alone or in combination with diuretics, but should avoid any CCB by the above-mentioned reason.

4. AUTOPSY FINDINGS

Autopsy was performed 5 hours after death. The cadaver was cachexic with a body weight of 35 kg.

The Pancreas:

A tumor measuring 3 cm in diameter was found in the head of the pancreas. On the cut surface of the tumor, a large cystic lesion containing mucin and tumor growth on its wall was observed in the center of the tumor and mucinous nodules in the surrounding tumor tissue (Fig. 3). The tumor invaded through the duodenal wall forming a cancerous ulcer near the Papilla of Vater. Infiltration into the wall of the common bile duct was also apparent, but no exposure of the carcinoma on the mucosal surface and no stricture of the duct were observed. Histopathological examination confirmed that the tumor was invasive ductal carcinoma of mucinous carcinoma subtype. The tall columnar epithelium with less atypical nuclei formed duct-like structures, small nests or muconodules in the stroma-rich tumor tissue. There was no immunohistological evidence for the expression of gastrin or gastrin-releasing peptide by tumor cells. The rest of the pancreas, the body and tail, was quite atrophic due to chronic pancreatitis. The presence of both the dilated ducts in the fibrotic stroma and the

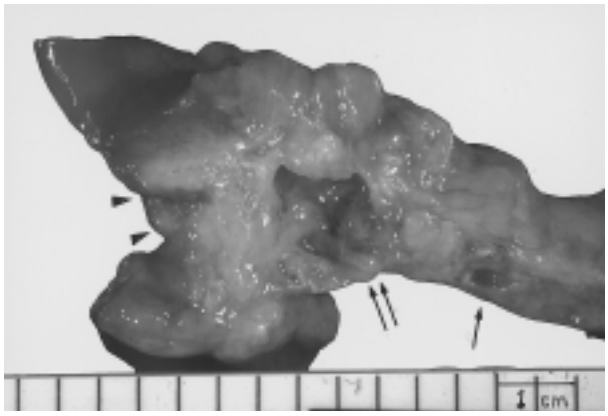

Fig. 3. Macroscopic appearance of the cut surface of the pancreas cancer. A large cyst (arrows) with tumors in its wall is observed in the center of the tumor. A smaller cyst (arrow) derived from pancreatic duct is also seen in the non-neoplastic region of the pancreas. Arrow heads indicate ulceration of the duodenal wall by invasion of a carcinoma.

mucinous cystic tumor indicate that occlusion of the main pancreatic duct by carcinomatous growth is the cause of near-total loss of acini by severe chronic pancreatitis.

Upper Alimentary Tract:

There was no mucosal defect except an erosive change observed in the restricted area of the esophago-cardiac (EC) junction and an ulcer by carcinoma invasion in the second portion of the duodenum. The squamous epithelial layer of the esophagus was slightly hyperplastic and gastric mucosa was well preserved. Since parietal cells with their characteristic eosin-stained cytoplasm were quite conspicuous in the histological specimen of the body of stomach (Fig. 4), the specimen from EC junction to the pyloric ring along the lesser curvature of the stomach were prepared to examine for the presence of hyperplasia of parietal cells. The fundic grand-region and transitional region extended far into the antrum, but the thickness of the glandular layer was within the normal range. Since the presence of plump cytoplasm and cells with double nuclei among the parietal cells was suggestive of active function of these cells, morphometric analysis was subsequently performed and hyperplasia of these cells was clearly shown (Dr. Watanabe, Kobe University School of Medicine).

G cells detected by enzyme-immunohistochemical technique using anti-gastrin antibody (DAKO) were

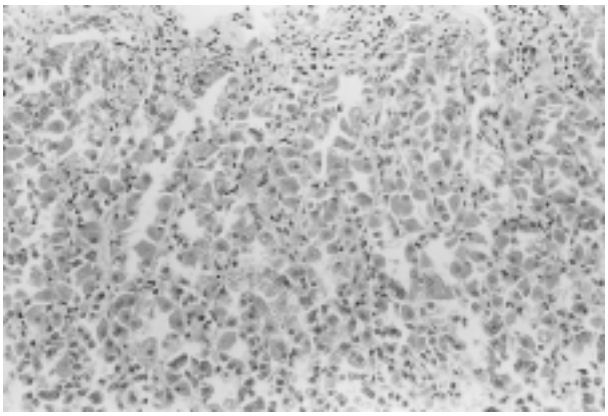

Fig. 4. Histopathology of the mucosa of the fundus of the stomach. Presence of parietal cells with characteristic plump cytoplasm but not other types of glandular epithelium is apparent. The number of parietal cells in the mucosa but not the thickness of the mucosa is increased.

quite characteristic based on their abundant cytoplasm and strong immunostaining (Fig. 5) compared with those in the control specimen. However, precise counting of gastrin-positive cells in the specimen covering the area from EC-junction to the pyloric ring revealed a lack of increment in the number of G cells compared with nine control stomach tissue samples (Dr. Watanabe). In addition, there was no change in the distribution of G cells and no small-sized endocrine tumor in the duodenum.

Prominent hyperplasia of parietal cells concurred with the clinical laboratory data and clearly explained the presence of hypergastrinemia. Since morphometric and histopathological examination showed no hyperplasia of G cells in the antral region or gastrinoma in the pancreas or the duodenum, hypergastrinemia should be the result of

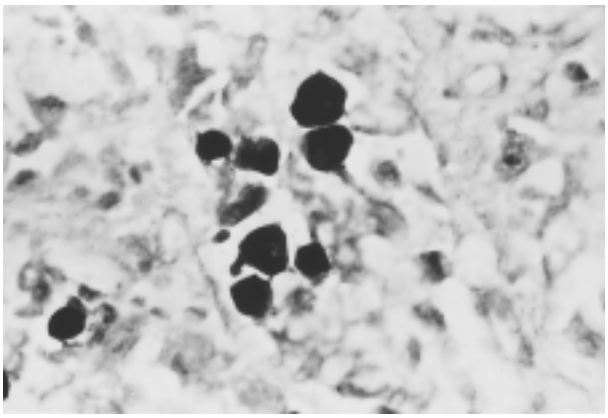

Fig. 5. Immunohistology of gastrin containing cells. G-cells shown are characteristic with their large cytoplasm.

hyperfunction of G cells. Although quantitative interpretation of the result of immunohistochemistry is limited, the presence of G cells with abundant cytoplasm and strong immunostaining is an indirect evidence for the enhanced hormone production by these cells. Whether there was an associated production of stimulating factors or defective regulatory system controlling gastrin production remains to be determined. Production of gastrin-releasing peptide by pancreatic carcinoma cells examined by an antibody from DAKO could not be identified, and infection by *Helicobacter pylori* could not be confirmed in the gastric mucosa. Slow passage of the gastric content due to the carcinoma invasion of the duodenum might be one of the stimulating factors. Finally, it is important to indicate that autopsy findings included a gastro-intestinal mucosa that was well protected from the offensive factors by medication used during treatment.

The Liver and Biliary Tract:

A localized peritonitis was noted around the gall bladder. Acute cholecystitis and cholangitis were also apparent. The liver weighed 1,080 g and was very soft. Macroscopic examination of the cut surface showed an edematous portal area, staining of the liver tissue surrounding the portal by bile color, and small cyst-like structure and abscesses distributed in the liver parenchyma. Histopathological examination showed pericholangitis with necrosis of the bile duct epithelium as well as inflammation of whole Glisson's sheath with prominent edema and inflammatory cell infiltration extending into the liver lobules resulting in the formation of small abscesses. The whole hepatic cord was quite atrophic and hepatocytes were degenerative.

The Spleen:

The organ was soft and swollen and weighed 140 g. A large amount of splenic exudate characteristic of acute splenitis was observed and this was confirmed by reaction of neutrophils in the histopathological specimen.

Direct Cause of Death:

The direct cause of death was considered to be septic shock caused by retrograde infection of the

liver through the biliary tract. The pathological findings of the liver and spleen support this conclusion, together with the lack of inflammatory lesions in the lung apart from localized foci not sufficient to cause respiratory disturbances. Although there was no stenosis or occlusion of the pancreatic part of the common bile duct, external pressure by the carcinomatous mass against the duct system might have caused persistent disturbance of bile flow, thus providing a condition that could lead to retrograde infection.

Pathological Diagnosis:

1. Pancreatic cancer; pancreas head, solid type, invasive ductal carcinoma, mucinous carcinoma.
2. Chronic pancreatitis.
3. Acute cholecystitis, localized peritonitis around the gall bladder, and acute cholangitis.
4. Pericholangitis and inflammation of the portal area, micro-abscesses in the liver, and degeneration of hepatocytes, liver weight 1,080 g.
5. Acute splenitis, spleen weight 140 g.
6. Hyperplasia of the gastric parietal cells due to hypergastrinemia.

5. RECOMMENDED READINGS

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2) Norton JA, Fraker DL, Alexander RH, *et al*. (1999) Surgery to cure the Zollinger-Ellison syndrome. *N Engl J Med* 341: 635-644.

(Summarized by Kinoshita Y, Okunishi H, and Harada T).

6. STUDENTS AND INSTRUCTORS

Students in charge of this case

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